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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/693,315	10/24/2003	Takao Abe	AM 100905 P1 (0036119.002	1495

49598 7590 04/12/2006

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EXAMINER	
BERCH, MARK L	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 04/12/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/693,315	ABE ET AL.	
	Examiner	Art Unit	
	Mark L. Berch	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6 and 8-42* is/are pending in the application.

4a) Of the above claim(s) *31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,8-30 and 32-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10-24-2003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-6, 8-30, 32-42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "organic tertiary base" is indefinite. Tertiary what? Would this cover isopropyl amine, which has a tertiary carbon?

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-6, 8, 12, and 41--42 rejected under 35 U.S.C. 103(a) as being unpatentable over EP 232966, alone or in view of McOmie or US 4891369, and also in view of 6268393, Kashima, Nagao, Evans, Crimmins, Brown, Fukuzawa, or Mukaiyama.

In the primary reference, see Step F1 on page 20, along with the detail on page 24, and Formula IC on page 12. A specific example of this type of compound is seen on page 30, example 25. For the second, step, which is the elimination step, applicants use triphenyl

phosphine. This is taught by the reference at page 25, line 2. Alternatively, the claim calls for the use of an anhydride; such is seen at examples 30-31, and the use of the acid chloride is seen in ex 32. Although the intermediate compound which applicants call 19, the acylated hydroxy, is not identified in these steps, that m product is presumed to have been made because these are the reagents which make it. Further, example 29 has the intermediate product identified as this reaction was done without the elimination step, showing the acetate. There are two differences.

A. The starting material of the prior art differs from the starting material here in that it has a slightly different protecting group. That is, it has for R4 the protecting group p-methoxybenzyl whereas the claim has p-nitrobenzyl. However, the reference teaches that these are both suitable for the purposes on the invention. The sentence on page 10, lines 48-55 lists both groups. Thus, any compound formed from any of the protecting groups on this list would be obvious variants of the species which appears in the reference.

Further, the secondary references McOmie or US 4891369 teaches the advantage of using the p-nitrobenzyl. One of ordinary skill in the art of synthetic chemistry would know, and McOmie teaches, that the p-nitrobenzyl groups is more stable to acids than is the p-methoxybenzyl group used in the reference, giving a clear motivation for its use. This exemplified in the 4891369 reference, which says (Column 8, lines 13-20) "Especially when the penicillin carboxyl-protecting group represented by R is ... p-nitrobenzyl or the like, the deesterification is advantageously conducted by reduction. When the protecting group is p-methoxybenzyl ... the reaction is advantageously carried out using an acid." Applicants must show unexpected effects arising from the use of one para-substituted benzyl rather than another to overcome this rejection.

B. The aldol condensation is done with a slightly different procedure. EP 232966 uses Lithium amide bases. The current claims use an "organic tertiary base" (whatever that is), plus a Lewis acid, e.g. Mg salt. The 6268393 reference teaches exactly such an equivalence in an aldol reaction. In 6268393, see paragraph bridging columns 22-23, which states that instead of LDA (lithium diethyl amide), other bases such as amines can be used; and MgBr2 appears as an auxiliary at column 23, line 4. A similar teaching appears as the first full paragraph in Column 27. This is the exact variation that applicants employ. Thus, such a variation is obvious. Note that the diisopropyl ethyl amine which is named in claim 4 is named in this reference as well. In Kashima, the reaction is run both ways. See Table 1, with LDA in the first column of results and $MgBr_2$/DIEA in the third. While the yield results were sometimes fairly similar, sometimes the $MgBr_2$/DIEA results were significantly better, e.g. the first one, 91% vs 69%, or the third from last 83% vs 50%. Taken as a whole, the $MgBr_2$/DIEA results were better 7 times, the LDA were better 2 times, and thus one is motivated to use the technique that tends to give better yields. In Nagao, see Scheme 1, where the Lewis acid is a tin triflate, and the base is ethyl-piperidine. In Evans, see Table 1, where the acid is Magnesium dichloride and the base is triethylamine. In Crimmins, see Scheme 3, which uses TiCl4 as Lewis acid and DIEA or TMEDA, and in Scheme 4, where the base used was sparteine. In Brown, see last paragraph of the experimental section, which uses dialkyl and dicylcoalkyl Boron halide as the Lewis acid, and triethylamine as the base. In Fukuzawa, see Scheme 1, and note the amines used in Table 1, and the fact that the Yb-triflate is the Lewis acid. In Mukaiyama, see the two schemes, which use tin triflate and two tertiary amines.

Many more such references could be cited. The Lewis acid/tertiary amine system (sometimes called "soft enolization") is entirely conventional.

With regard to the chilling of claim 5, see primary reference, line 22. The heterocycles of claim 12 are provided for at page 8, lines 1-23.

With regard to claims 41-42, the same applies, except that point A is not a difference, since these claims, unlike claim 1, do permit the p-methoxybenzyl group.

The traverse is unpersuasive. Applicants point to the fact that the starting material is "a crystalline derivative", and that unexpected effects flow from that. The claim has no such limitation. Patentability cannot be based on limitations not actually present in the claims. Second, applicants assert that their protecting group "permits reductive elimination and deprotection to take place in a single step, rather than a two-step procedure as can be followed for compounds having other protecting groups." This is unsound reasoning. A two step process also "can be followed" for applicants compounds as well. The specification does not say, nor do the remarks say, that reductive elimination and deprotection cannot be done in a single step for the prior art protecting group as well. If applicants were asserting that their protecting group could permit something to be done that the prior art protecting group could not do, that would be one thing, but applicants are deliberately stopping short of that, presumably because it simply is not true. Second, even if this were true, applicants have not asserted that this is an unexpected difference, let alone presented any actual reasoning that it is an unexpected difference. Indeed, if true, this would appear to be an expected difference, as the properties of protecting groups are generally well known. Expected differences are not evidence of unobviousness, In re Gershon, 372 F.2d 535, 538, 152 USPQ 602, 604 (CCPA 1967); Ex parte Blanc, 13

USPQ2d 1383; In re Merck & Co., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). This issue is under prosecution in the parent application and will presumably be decided by the Board of Patent Appeals and Interferences.

Second, applicants argue that there is no reasonable expectation of success because the secondary references do not show the "aldol condensation of a ketone that is within a constrained ring", referring to the β-lactam ring. First, this is not a ketone, it is an amide. Additional references (Kashima, Nagao, Evans, Crimmins, Brown, Fukuzawa, or Mukaiyama) are now cited, showing that that particular procedure, has been used for an assortment of substrates, although most of these are in fact amides (see e.g. 10 of Kashima, 6 of Nagao, etc.) Applicants point to the "constrained ring", but it is not clear why that should be of any relevance. The "soft enolization" technique here uses an organic amine, e.g. triethylamine, which is much milder than the LDA used in the primary reference. Thus, there is every reason to expect that if the ring survives the LDA, it would survive the milder triethylamine. As for the Lewis acid, there is no reason at all to expect that it would harm the ring, since such acids are routinely used for manipulation of substituents on β-lactams.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 1-6, 8-30, 32-42 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-31, 33-40 of copending Application No. 10427666. Although the conflicting claims are not identical, they are not patentably distinct from each other because this is essentially the same process involved as is present in the parent case.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

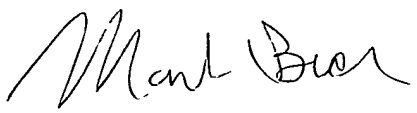
Claims 1-30, 32-42 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and others of copending Application No. 10427427. Although the conflicting claims are not identical, they are not patentably distinct from each other because this is essentially the process for making the compounds of 10427427. There is ordinarily no patentable distinction between compositions of matter and methods. Hence, in the absence of a Terminal Disclaimer, an obviousness-type Double Patenting rejection may be made. See *In re Boylan,* 157 USPQ 370 , Ex parte MacAdams, 206 USPQ 445; *Geneva Pharmaceuticals Inc. v. GlaxoSmithKline PLC,* 68 USPQ2d 1865 (CA FC 2003).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark L. Berch whose telephone number is 571-272-0663. The examiner can normally be reached on M-F 7:15 - 3:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on (571)272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Mark L. Berch
Primary Examiner
Art Unit 1624

4/10/2006